

## ARCHIMEDES

## Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family.<sup>1</sup> *Archimedes* seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the *Emergency Medicine Journal*—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What *Archimedes* offers are practical, best evidence based answers to practical, clinical questions.

The format of *Archimedes* may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,<sup>2</sup> and gaining answers.<sup>3</sup>) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question.<sup>4</sup> A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett<sup>5</sup> and Moyer<sup>6</sup> may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published *Archimedes* topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site ([www.bestbets.org](http://www.bestbets.org)) and may be of interest to paediatricians include:

- What dose of dexamethasone should we use in croup?
- Is neonatal cranial ultrasound a useful predictor of longterm neurodevelopmental outcome in preterm or low birth weight infants?
- Is monteleukast useful in the treatment of bronchiolitis?

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at [www.bestbets.org](http://www.bestbets.org). If your question still hasn't been answered, feel free to submit your summary according to the Instructions for Authors at [www.archdischild.com](http://www.archdischild.com). Three topics are covered in this issue of the journal.

- Do well infants born with an isolated single umbilical artery need investigation?
- In a preterm infant, does blood transfusion increase the risk of necrotising enterocolitis?
- Are routine urine cultures helpful in the management of asymptomatic infants or preschool children with a previous urinary tract infection?

**Decision analysis**

When we make a decision about a course of action—a diagnostic test, treatment, or other intervention—we weigh up more than just a single outcome. There could be beneficial outcomes, but the possibility of negative effects (adverse events, failures, repeat attendance, and so on) also needs to be considered. Diagnostic tests may give the wrong answer, and expose the patient to risks of non-treatment (or of inappropriate treatment). As clinicians, we instinctively assess the chances of the outcomes, weigh them, and conclude on a course of action.

For example, in treating a sick child with pneumonia, one may use oral co-trimoxazole, an oral beta-lactam, intravenous penicillin, or intravenous cefuroxime. What is the best treatment to use? What does best mean: Most cures? Fewest side effects? Most cost effective? Most comfortable? There may be variations based on where you're working—Australia or America, a rural clinic in the Kimberley or urban Adelaide hospital. Individual factors—allergy, HIV co-infection, likely support from parents—can all contribute to the decision.

Decision analysis is a way of modelling all the factors and formally adding up the likely outcomes, and weighting these with values—be these costs, clinician, or patient centred measures of benefit (utilities). (See a previous *Archimedes* issue, “Economic analyses”<sup>1</sup> for more on “utilities”.)

For the clinician the full process can be difficult, time consuming, and monumentally boring. Where the practitioner can use such information is in taking analyses which have already been performed, appraising them, and using them in local practice.

If no analysis exists, it may be worth doing a “back of the envelope” analysis. Knowing how good your current treatment is (taking costs and adverse effects into account) will let you know how effective a new treatment has to be to beat it. If you're looking for a bedside diagnostic test, knowing in advance how many false negative and false positives you will accept informs you of the magnitude the likelihood ratios<sup>2</sup> will need to reach. If the target you've set is unfeasible, then the five minutes spent thinking this through may have saved you hours of work.

Now, it is stressed that decision analyses are models—not real. They provide approximations and guesses, and make transparent what occurs instinctively. In doing this, they make the decision process open to critical appraisal, rather than the decider open to criticism.

**References**

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Additional information on each of the topics is available on the ADC website ([www.archdischild.com/supplemental](http://www.archdischild.com/supplemental))

## Do well infants born with an isolated single umbilical artery need investigation?

### Report by

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You are the paediatric house officer performing discharge examinations on the postnatal ward. You are informed of this term neonate whose umbilical cord was noted to have a single umbilical artery (SUA) at delivery. He is otherwise well. You cannot detect any abnormalities on physical examination. Historically, SUA has been said to be associated with congenital malformations of different organ systems. You wish to appraise the evidence whether or not this infant needs investigations to detect associated malformations.

### Structured clinical question

In a term neonate with no other obvious congenital malformations [patient] does the presence of a single umbilical artery [risk factor] necessitate further investigation [intervention] to exclude associated malformations [outcome]?

### Search strategy and outcome

Primary source: Medline via Pubmed using keyword "umbilical artery". A total of 477 individual articles were found. This was limited to 152 articles by selecting those in English language and human studies relating to neonates (birth-1 month). The search was verified by using (MeSH) subject heading: "umbilical artery" + subheading: abnormalities. Individual abstracts were read. A systematic review with meta-analysis of the relevant studies which matched our structured clinical question was found. The meta-analysis and original articles of seven relevant included studies were appraised.

Secondary sources: Cochrane database and Best Bets. No further papers were identified.

See table 1.

### Commentary

Single umbilical artery has long been recognised as a soft marker for chromosomal abnormalities and congenital

malformations. Autopsy series from aborted and still born fetuses report a high incidence of associated malformations. It is therefore conceivable that if SUA is detected in a neonate with obvious physical abnormalities, full investigatory work up to detect occult malformations of various organ systems has to be undertaken. Nevertheless, in many cases SUA can be an isolated feature. It is unclear if apparently asymptomatic infants with SUA need to be investigated.

The meta-analysis cited<sup>1</sup> was a review of 37 studies published over the past 40 years. Eleven of the 37 studies were performed on specimens obtained from autopsy studies of abortus and stillborn babies. These were not relevant to our question. In the remaining 26 studies, the diagnosis of SUA was made by clinical examination of the placenta or umbilical cord after delivery and thus satisfied our initial criteria. But in only seven of these was there data for asymptomatic isolated SUA. Overall, a mean of 16.2% of infants with isolated SUA had a renal anomaly (median 5.3%). In half these cases (8%) these malformations were severe and persistent on follow up. The most frequent major renal anomaly was vesico-ureteric reflux, grade 2 or greater, in 2.9% of the total population.

In the study by Bourke and colleagues,<sup>2</sup> infants with isolated SUA had a screening ultrasound scan. Those with abnormal scans underwent a micturating cystourethrogram and urine cultures. Vesico-ureteric reflux (VUR) was documented in 4.5% of these infants. It is interesting to note that three of the five infants with VUR developed urinary tract infections (UTI) within the first five months of life.

The incidence of occult renal anomalies in the general paediatric population is about 2.5%;<sup>9</sup> the prevalence of VUR in healthy individuals is unclear. Ransley,<sup>10</sup> in a compilation of several publications, reports a rate of 1.3%. From the currently available evidence it seems that the incidence of silent renal abnormalities in infants with isolated SUA is at least threefold higher for severe malformations and sixfold higher for any renal malformation compared to the general paediatric population. VUR is probably up to three times commoner in these infants. A screening renal ultrasound scan may be useful in detecting occult structural malformations of the urinary tract. However, its positive predictive value in suggesting VUR was low; it was reported as 32.5% in a recent study.<sup>11</sup> As VUR and UTI are believed to be forerunners of reflux nephropathy, it seems prudent to investigate infants born with an isolated SUA by means of a micturating cystourethrogram (MCUG) and maintain a low threshold to diagnose and treat urinary tract infections.

### CLINICAL BOTTOM LINE

- There is an increased proportion of significant occult renal malformations in asymptomatic infants born with an isolated single umbilical artery (8% total population).
- A significant proportion of such infants may have vesico-ureteric reflux (grade 2 or worse).
- Screening renal ultrasonography and micturating cystourethrography are useful investigations to detect associated renal anomalies in these cases.
- There is a lack of data regarding malformations of other organ systems in infants with asymptomatic isolated SUA.

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**Table 1** Do well infants born with an isolated single umbilical artery need investigation?

Citation	Study group	Level of evidence	Outcome	Key results	Comments
Thummala <i>et al</i> (1998)	204 infants with isolated single umbilical artery from 7 studies where in infants with isolated single SUA were investigated for occult renal malformations	Meta-analysis of case series (level 3a)	Detection of associated malformations	33/204 infants had occult renal malformations Mean 16.2%, (95% CI for mean 7.7% to 25.6%; Median 5.3%; (range 0% to 33%) 15/204 had major anomalies (7.4%) The most frequent renal anomaly of significance was vesico-ureteric reflux	None of the case series included had controls Only articles in English language were included in the meta-analysis There is no data on other organ system malformations
Bourke <i>et al</i> (1993)	Prospective case series of 112 infants with isolated SUA from 35 000 deliveries. Case detection was by clinical examination of the placenta All cases underwent screening renal ultrasonography. Those with abnormalities were further investigated with a micrurating cystourethrogram (MCUG) and had monthly urine cultures for 6 months	Case series (level 4)	Urinary tract anomalies detected on ultrasonogram	19/112 had some form of renal anomaly (16.9%). In 8 of them the abnormalities were significant (7.1%). 5/8 had VUR. 3/8 infants had UTI within the first 5 months of age	Included in Thummala paper Does not specify if deliveries were consecutive No control group
Leung and Robson (1989)	Case series of 159 infants detected to have SUA from records of 56 919 deliveries during a 20 year period. 27 of these 159 infants who had an isolated SUA underwent renal imaging.	Case series (level 4)	Urinary tract anomalies detected on ultra sonogram or intravenous pyelography (IVP)	5/27 had abnormal renal imaging (18.5%) One each had multicystic kidneys, hypoplastic kidneys, horse shoe kidneys, hydronephrosis and bifid ureter	Included in Thummala paper Retrospective review Screening tool not the same for all cases No control group
Feingold <i>et al</i> (1964)	Prospective case series. 32 infants detected to have SUA among 6080 deliveries. Three infants died in the neonatal period. IVP was performed on 24 of the 29 survivors without overt renal malformations	Case series (level 4)	Urinary tract anomalies detected on IVP	8/24 infants; ( 33.3%) had renal malformation In half of them malformations were severe These included massive reflux with hydronephrosis, absent kidney, horse shoe kidney and severe bladder neck obstruction	Included in Thummala paper Not all cases were investigated No control group
Vlietinck <i>et al</i> (1972)	Prospective case series without controls. 29 infants were detected to have SUA among 2572 deliveries. 4 were stillborn and 2 died in the neonatal period. 19 of the 23 infants who had an isolated SUA were investigated	Case series (level 4)	Urinary tract anomalies detected on IVP	1/19 infants (5.3%) had an abnormality—complete duplication of the left renal pelvis	Included in Thummala paper Not all cases were investigated No control group
Harris and Van Leeuwen (1968)	Prospective case series without controls. 11 infants detected to have isolated SUA among 2800 consecutive deliveries	Case series (level 4)	Urinary tract anomalies detected on IVP	None of the infants had renal malformations (0/11)	Included in Thummala paper Small sample size No control group
VanLeeuwen <i>et al</i> (1967)	Prospective case series without controls. 4 infants were detected to have isolated SUA among 2000 consecutive deliveries	Case series (level 4)	Urinary tract anomalies detected on IVP	None of the infants had renal malformations (0/4)	Included in Thummala paper Small sample size No control group
Johnsonbaugh (1973)	Prospective case series. 8 infants of 1152 deliveries had isolated SUA. Only 5/8 infants were investigated	Case series (level 4)	Detection occult renal anomalies by IVP, transumbilical artery aortography to detect aortic malformations and chromosomal analysis	None of the 5 investigated infants had renal, aortic malformations or any chromosomal abnormality	Included in Thummala paper Not all cases were investigated Small sample size No control group

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# In a preterm infant, does blood transfusion increase the risk of necrotizing enterocolitis?

## Report by

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An otherwise well 3 week old infant born at 28 weeks gestation has a haemoglobin level of 68 g/l and is prescribed a blood transfusion. The departmental protocol states feeds should be withheld during the transfusion to decrease the risk of development of necrotising enterocolitis (NEC). What is the evidence that blood transfusion increases the risk of NEC?

## Structured clinical question

In a preterm infant [patient] does blood transfusion [intervention] increase the risk of NEC [outcome]?

## Search strategy and outcome

Search words: "transfusion" AND "necrotizing enterocolitis" (excluding exchange transfusion).

Secondary sources—Cochrane Library (Issue 3, 2003): no relevant systematic review.

Pub Med (1975–2003). Limits: newborn. Search outcome: 85 articles, of which two were relevant.

Pub Med (1975–2003) using clinical queries with methodology filters (category aetiology, emphasis: sensitivity). Limits: newborn. Search outcome: 34 articles, of which one was relevant (already retrieved by Pub Med).

Embase (1974–2003). Search outcome: 111 articles, of which one relevant (already retrieved by Pub Med).

Cinahl (1982–2004). Search outcome: 15 articles, none relevant.

Sum Search. Search outcome: 29 articles, none relevant. See table 2.

## Commentary

In the two reported studies,<sup>1, 2</sup> the indications for transfusion were not standardised, the time interval between transfusion and NEC was not available, and any transfusion at any time between birth and NEC was analysed.

The results of the ecological study<sup>1</sup> are difficult to interpret as the association found between transfusion and NEC was at the level of the NICU but was not studied at the individual neonate level.

Bias in the published results of the two studies is possible, as the findings may be related to other practices in the specific neonatal intensive care unit (e.g. restricted transfusion policy). It may also reflect confounding by the indication for transfusion (e.g. infants who have NEC may require more transfusions). It could also be that the anaemia for which a blood transfusion was requested was an independent risk factor for NEC, or an early manifestation of NEC still developing, which then becomes recognised several hours later (during or after the transfusion).

While anecdotal reports suggest that NEC has developed quickly after a blood transfusion, such information is not available in published studies. However, neonatal exchange transfusion<sup>3, 4</sup> and intrauterine transfusion,<sup>5</sup> both via umbilical vessels, have been shown to be associated with an increased incidence of NEC.

Further studies minimising bias and confounding are needed to prove or disprove an association between blood transfusion and the risk of NEC, but even then, association is not necessarily synonymous with causality. It should be possible to undertake randomised controlled studies on the

**Table 2** Blood transfusion and necrotising enterocolitis

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Bednarek <i>et al</i> (1998)	Prospective analysis of blood transfusions and outcomes (including NEC) in 825 very low birth weight (<1500 g) infants in 6 neonatal units over 1 year, with adjustment for birth weight and illness severity. The 6 units were categorized into low, medium and high transfusion units based on the mean number of transfusions per infant	Prospective ecological study (level 2c)	Incidence of NEC	Adjusted OR (95% CI) for the: High transfusing units: 1.1 (0.5–2.2) Medium units: 1 (reference) Low transfusing units: 0.3 (0.1–0.08) p<0.05 The low transfusing NICU group showed a significantly lower incidence of NEC compared with the middle and high transfusing units.	Association difficult to interpret in ecological studies as the association found between transfusion and NEC is at the level of the units but was not studied at the individual neonate level Findings may be related to other practices in the specific NICU (e.g. restricted transfusion policy) or reflect confounding by indication for transfusion (e.g. infants who have NEC may require more transfusions). Time interval between transfusion and NEC not available (any transfusion at any time before NEC was counted)
McGrady <i>et al</i> (1987)	Case-control study of 33 neonates with NEC during an outbreak, and 40 controls matched on birth weight, duration of stay in the unit and approximate date of admission. Median birth weight of cases = 1360 grams, median gestational age = 32.5 weeks	Individual case-control study (level 3b)	Risk factors for NEC	Transfusion was highly and significantly associated with NEC, crude OR = 15.5 (95% CI = 2.59–92.51); RR = 8.98 (95% CI = 1.08–74.6) after adjustment for therapy with caffeine, theophylline and furosemide. There was no association with type or timing of feeding	This study was that of an outbreak of NEC and not the endemic form of NEC. Epidemic NEC may be importantly very different from endemic NEC

effect of withholding feeds versus feeding during blood transfusions on the rate of NEC, although blinding would be impossible and the sample size required for adequate power would likely be extremely large.

#### CLINICAL BOTTOM LINE

- Low quality evidence has shown an association between neonatal blood transfusion and the development of NEC.
- Withholding enteral feeds for a few hours during a blood transfusion may have theoretical benefits, but there is no published evidence to support this practice.
- Despite a lack of direct evidence, we continue to withhold feeds during blood transfusion.

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## Are routine urine cultures helpful in the management of asymptomatic infants or preschool children with a previous urinary tract infection?

Report by

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An asymptomatic 18 month old boy, undergoing radiological investigations after a urinary tract infection (UTI) diagnosed few months earlier, is reviewed at the clinic. According to departmental protocol, a three monthly urine culture should be submitted in infants and young children as, until the age of 4 years, they remain at risk of developing renal scars after UTIs. You wonder as to the value of this routine culture.

#### Structured clinical question

In an asymptomatic infant or preschool child with a history of UTI under 4 years of age [patient] does the detection and management of asymptomatic bacteriuria (ABU) on routine urine culture [intervention] decrease the incidence of symptomatic UTI or renal scarring [outcomes]?

#### Search strategy and outcome

Secondary sources—Cochrane Library (Issue 3, 2003): search words: (1) “urine culture” OR (2) “asymptomatic bacteriuria” OR (3) “urinary tract infection”. Database of systematic reviews: 32, 24, and 135 articles (for 1, 2, and 3 respectively), with 24, 14, and 101 complete reviews (for 1, 2, and 3 respectively). No relevant systematic review for under 4s.

PubMed (1975–2003): search words—(“urine culture” OR “asymptomatic bacteriuria” OR “urinary tract infection”) AND (“prognosis” OR “renal scar\*”). Limits: child <4 years. Search outcome: 12 papers, of which two were relevant (under 4 years of age).

SumSearch: 43 articles, two relevant (already retrieved by PubMed).

See table 3.

#### Commentary

As infants and young children are thought to remain at risk, until the age of 4 years, of developing renal scars after UTIs, some paediatric departments carry out periodical urine culture in this group, even in the absence of symptoms. In addition to the fact that urine collection and culture in preschool children under 4 years of age is not always technically easy and is associated with an unsatisfactory high risk of bacterial contamination, detection of ABU in this group would be of value if its treatment results in decreased risk of renal scarring and symptomatic UTI, without adverse effects of the therapy.

Previous reports have shown that the development of new renal scars or the progression of existing scars are very uncommon after the age of 4 years,<sup>3</sup> and, although new scars may occasionally develop after the age of 4 years, they generally occur in the context of symptomatic UTI or acute pyelonephritis but not after ABU.<sup>4</sup> Although there is evidence of progression of scarring in relation to ABU, there is no evidence of benefit from treatment. Studies of ABU in schoolchildren have shown that absence of treatment does not increase the risk of subsequent renal scarring after the age of 5 years<sup>5</sup> and that bacterial strains in ABU do not commonly cause symptomatic pyelonephritis.<sup>6</sup> However, changes in bacterial flora have been associated with recurrences of or development of acute pyelonephritis ABU.<sup>7</sup> In children with ABU, the use of antibiotic therapy for intercurrent infections leads to a change in the urinary flora and is associated with an increased risk of pyelonephritis,<sup>8</sup> in contrast to untreated ABU where no spontaneous changes of urinary bacteria occurs.<sup>9</sup>

We therefore reviewed all published studies to try answering specifically the structured clinical question: What is the evidence that the detection and management of ABU in preschool children under 4 years of age decrease the incidence of symptomatic UTI or renal scarring? Unfortunately, we found no good quality randomised studies addressing that specific question. The two studies reviewed show that in children under 4 years of age, no new renal scarring occurred when bacteriuria was asymptomatic<sup>1</sup> and that renal scarring only occurred in children with symptomatic recurrences associated with abnormal cystograms.<sup>2</sup> However, both studies have obvious weaknesses: in addition to small sample sizes, there was no treatment randomisation. The first study was carried out in an unselected population of children, but not after a selected group with previous UTI which would very likely have a different natural history and prognosis. The second study was carried out exclusively in girls, who are known to have a different natural history than boys. In addition, as these studies were carried out before DMSA was available, the diagnosis of renal damage was made by intravenous urography (IVU). As DMSA is more sensitive than IVU to detect cortical scarring, some small scars may not have been recognised on IVU, although such small scars are not thought to be clinically significant. In addition, the first study did not clearly differentiate between primary and secondary (after a previous UTI) ABU.

Despite their weaknesses, which should caution about the generalisation of their findings, these studies have shown that the detection and the treatment of ABU in infants and preschool children did not decrease the risk of renal scarring. In addition,

**Table 3** Value of routine urine cultures in asymptomatic children with a previous history of UTI

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Wettergren <i>et al</i> (1990)	Unselected population of 50 patients (14 girls) under 1 year of age with bacteriuria on screening, verified by suprapubic aspiration and untreated. Follow up for up to 6 years	Prospective cohort (level 4)	1. Subsequent periodical urine cultures during the follow up period 2. Measurement of renal parenchymal thickness and renal surface area on IVU at 3 years	1. Two infants developed pyelonephritis within 2 weeks of diagnosis of ABU. ABU recurred in 10 children* 2. No child (0/36) developed new renal damage. IR=0 (95% CI=0 to 0.09)*	Unselected population of well infants (not after acute UTI) Screening of bacteriuria primarily detected innocent bacteriuria and was not recommended.
Randolph <i>et al</i> (1975)	25 girls under 6 months of age with bacteriuria, followed up with cultures up to 6 years of age. No chemoprophylaxis but treatment of individual episodes	Prospective cohort (level 4)	Development of UTI and renal scarring (IVU) during the follow up period	1. Although described as ABU, initial episodes were always symptomatic (lower tract symptoms). No scars on initial IVU 2. Recurrences in 9 infants, always asymptomatic (lower tract symptoms) 3. New scarring developed in 3 children, all of whom had recurrences (symptomatic) and evidence of reflux, bladder trabeculation and urethral stricture. No recurrences after 3 years of age and no new scars at 6 years	Study exclusively in girls, natural history in boys may be different Even in ABU, signs of lower UTI were evident to the "instructed parents"

\*In view of study design (prospective cohort), risk reduction and NNT could not be calculated.

antibiotic induced modifications of the bacterial flora may increase the risk of acute pyelonephritis, and therefore the risk of cortical damage. Therefore, the practice of routine detection of bacteriuria in asymptomatic infants and preschool children is not supported by evidence<sup>1,2</sup> and may even be harmful.<sup>7,8</sup> Future randomised double blind controlled studies, clearly differentiating between primary and secondary ABU, with outcomes based on DMSA, are recommended.

#### CLINICAL BOTTOM LINE

- There is no evidence to show that detection and treatment of ABU in infants and preschool children with a history of UTI decrease the risk of renal scarring.
- The benefit of routine detection and treatment of ABU in such children is not supported by evidence and may even be harmful.

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#### Announcement

##### Third International Congress on Shwachman-Diamond Syndrome 26–29 June 2005, Robinson College, Cambridge, UK

Papers are invited on the following topics:

Oral and poster presentations, discussion, roundtables

1. What have we learned about SDS? Clinical features; genetic diagnosis
2. Where are we now? Epidemiology; molecular biology; management of clinical problem: gastrointestinal; nutritional; blood & bone marrow; growth & skeletal; oral & dental; developmental & psychological
3. Where are we going? International collaboration; registries & databases; prospects for new treatments: genetic; immunogenetic; pharmacological

*Further information:* Vicky Milner, Procon Conferences Ltd, Tattersall House, East Parade, Harrogate HG1 5LT. Tel: +44 (0)1423 56448; fax: +44 (0)1423 701433; email: [vickym@procon-conference.co.uk](mailto:vickym@procon-conference.co.uk); [www.shwachman-diamondsupport.org](http://www.shwachman-diamondsupport.org)



## Towards evidence based medicine for paediatricians

Bob Phillips

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